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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/513,997	02/26/2000	John J. Harrington	5817-7Q	9509

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	09/513,997	HARRINGTON ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *108-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *108-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-27-2003 has been entered.

2. Claims 108-119 are pending in the instant application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 108-119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention broadly encompasses an in vivo method of over expressing a desired protein encoded by a desired endogenous gene or a portion thereof into a an animal by introducing a non-homologously recombinant cell in which a vector comprising a transcriptional regulatory sequence is integrated such that the transcriptional regulatory sequence of the vector is operably linked to the desired endogenous gene. Claims also recite practicing the method in a mammal or in a human.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification as filed provides general statements such as:

> Alternatively, the cell expressing the desired gene product can be allowed to express the gene product *in vivo*. In certain such aspects of the invention, the cell containing a vector construct of the invention integrated into its genome may be introduced into a eukaryote (such as a vertebrate, particularly a mammal, more particularly a human) under conditions favoring the overexpression or activation of the gene by the cell *in vivo* in the eukaryote. In related such aspects of the invention, the cell may be isolated and cloned prior to being introduced into the eukaryote.

(see page 8, lines 1-8); or

> whose existence was, prior to over-expression, unknown. The cells can be used to produce desired amounts of an expression product *in vitro* or *in vivo*. If

see page 10, lines 26-27); or

> Analogously, *in vivo* methods of production of a gene expression product may comprise, for example, (a) introducing a vector of the invention into a cell; (b) allowing the vector to integrate into the genome of the cell by non-homologous recombination; (c) allowing over-expression of an endogenous gene in the cell by upregulation of the gene by the transcriptional regulatory sequence contained on the vector; (d) screening the cell for over-expression of the endogenous gene; and (e) introducing the isolated and cloned cell into a eukaryote under conditions favoring the overexpression of the endogenous gene by the cell *in vivo* in the eukaryote. According to this aspect of the invention, any eukaryote may be advantageously used, including fungi (particularly yeasts), plants, and

(see page 51, lines 21-29).

Except these general statements, the specification does not provide any specific guidance for introducing the recombinant cells into an animal and how and under what conditions will the cells be maintained in an animal such that the desired endogenous gene over-expresses the protein. The specification does not reach any condition for maintaining the introduced recombinant cells in an animal such that over expression of the protein could be achieved in vivo. In summary the specification does not provide any specific guidance or description as to how step (e) of the claimed methods would have been carried out.

At the time of the invention, while there were examples of introducing a cell in any animal, or a mammal or a human, for therapeutic purposes such as for ex vivo therapy, or not-therapeutic purposes such as for producing antibody, such methods were not routine and the methods described in the art were specific methods for specific cells and could not be used in the instant invention or any other situation generally. For example, the art of ex vivo therapy was unpredictable whereas the method of producing an antibody by introducing a recombinant cell in an animal was not routine.

For example, in case of ex vivo therapy, claimed invention would encompass introduction of autologous, allogeneic and xenogeneic cells in an animal and at the

time of the invention, while introduction of autologous cells in an animal was known, introduction of xenogeneic or allogeneic cells was not routine. For example, Fred Gage (Nature 392:18-24, 1998) noted that for non-autologous cells, the most serious challenge is the destruction of cell implant by the host's immune system and that in xenografts, complement mediation is the major problem whereas the hyperacute rejection is the rapid and dramatic immunological response. The specification does not teach how to address the issues of hyperacute and complement mediation associated with the xenotransplantation of cells.

At the time of the invention, xenogeneic transplantation of any cells was not routine. Samstein et al (Samstein et al. Journal of American Society of Nephrology 12:182-193, 2001), reviewing the state of the art of physiologic and immunologic hurdles of xenotransplantation, summarized:

"Although the potential advantages of xenotransplantation generate enthusiasm, these advantages must be weighed against what may seem to be the daunting hurdles to the clinical application of xenotransplantation. These hurdles include the immune response of the recipient to the transplant, the physiologic limitations of the transplant, infection, and ethical concerns".

In summary at the time of the invention, the art of xenotransplantation was unpredictable and the specification does not provide any guidance how to address the issues of unpredictability in introduction of cells of xenogeneic origin in an animal and maintaining in the animal such that the desired endogenous gene is expressed in vivo.

In addition to unpredictability of xenogeneic transplantation, ex vivo gene therapy in general was unpredictable even when autologous or allogeneic cells were used. For example, recombinant hematopoietic stem cells transduced with retroviral vector when introduced in an animal expressed the recombinant gene at a very low undetectable levels (for example, Anderson Nature 392:25-30, 1998; Kay et al. PNAS 94:12744-12746, 1997). The review by Anderson describes the state of the art of gene therapy- ex vivo and in vivo at the time of the invention and supports the view that the art of ex vivo therapy was unpredictable particularly because expression of a desired gene introduced into an animal ex vivo could not be

achieved to a therapeutic level or the expression level was so low that it could not even be detected.

Second, introduction of cells into an animal for any non-therapeutic use, for example, producing antibody was not enabled because the specification as filed does not provide any specific guidance for practicing any non-therapeutic method and the methods taught in the art were different from the method claimed in the instant and the general teachings of the art could not be applied. For example, the arts by Brodeur, Kints, Stewart, Shaw, Chen, Garver, Bronson, McNiece, Treco, Ishihara et al could not provide enabling support for the instantly claimed method because these articles describe use of specific cells and the method steps used in these articles could not be compared to the method claimed. For example, Chen and Garver articles are examples of ex vivo therapy and as discussed above the art of ex vivo therapy was unpredictable. It is emphasized that the method of Chen and Garver teach injection of cells transfected with a retroviral vector that expresses an exogenous gene, which is not the same as a cell in which the expression of an endogenous gene has been activated by introducing an exogenous promoter. Therefore, the expression pattern of a retroviral gene cannot be compared to the expression of an endogenous under the control of an exogenous promoter. It is noted that Anderson et al discussed the unpredictability of gene expression from retrovirally transduced cells.

It is reiterated that even though cells of the instant invention may express a protein in vitro in culture, there is no evidence that these cells when introduced in an animal will still produce the protein, in view of the unpredictability of the art as discussed by Anderson and in view of the lack of any working examples or any specific guidance for practicing the claimed methods. It is noted that the claimed method encompass incorporation of any transcriptional regulatory sequence of any origin into any cell of any origin into any animal, including any mammal and a human. It is recognized in the art that the transcriptional regulatory machinery is not only distinct between prokaryotes and eukaryotes, even in eukaryotic cells the mechanism varies widely and there are tissue specific requirements for transcriptional regulation in an animal. For example, cell specific and tissue specific

nuclear matrix proteins and variants and modified histones are important for tissue and species specificity of ligand-induced response (see the abstract in Ruh et al. Crit. Rev. Eukaryot. Gene Expr. 6:271-283, 2000). This is just one example, of the complexity of in vivo gene expression in a eukaryotic animal and the claimed invention encompasses a very broad field of transcriptional regulation in vivo, but the specification does not provide any guidance for maintaining over expression of a gene in vivo when a recombinant cell is introduced in an animal. Because of the differences in producing the cells of the invention from those of the art, an artisan would not know whether the expression levels of the protein would be similar and therefore, it would be unpredictable whether the cells would produce any protein in vivo.

Regarding enablement of a claimed method for the use of producing an antibody, the method is not enabled because a method of antibody production is a specialized method with distinct steps, for example, production of a tumor cell line which when introduced in mouse produces a ascitic tumor, injection of tumor cells in a pathogen free mouse, development of the tumor in the mouse etc. And none of these methods are part of the claimed method and are not taught in the specification. Furthermore, it was not routine in the art to produce antibody and hybridomas in any mammal or a human as encompassed by claims 118 and 119. Additionally, teachings of making ascites tumor formation are irrelevant for practicing the claimed method in a human. So far as producing hybridomas are concerned, only certain mice, such as BALB/c mice are used, therefore any animal cannot be used for such a utility. Even if any animal could be used for such as utility, the method taught in the art, such as by Broduer et al would be irrelevant because the cells of the claimed invention cannot be compared with hybridoma cells.

It is reiterated that the specification except for single sentences regarding in vivo method does not provide how would an artisan of skill have practiced the claimed method. It is noted that since the cells used in the claimed invention are not related or similar to any other cells that are taught in the cited arts, the method

used in these other unrelated art cannot be used to support the enablement or other readily apparent utilities. The specification has failed to provide any evidence where in the specification how to make and use the claimed methods have been described. Pages 7-9, 13, 16, 17, 29 and 35 of the 08/941223 provide cursory statements, such as "Alternatively the cells can be allowed to express the desired gene product *in vivo*" (page 7, lines 8-9); "The cells can be used to provide desired amounts of a gene product in vitro or in vivo, The gene product can then be isolated and purified if desired. It can be purified by cell lysis or from growth medium (as when the vector sequence contains a secretion signal sequence)" (page 8, lines 14-17). Applicants are arguing that such statements provide enabling disclosure for the claimed methods, however, it is not clear how an artisan of skill would have been able to practice the claimed method by following these cursory general statements.

In conclusion, it is emphasized that the specification does not teach any specific teaching for carrying out any in vivo method and since the introduction of recombinant cells into an animal for over expressing a protein was not routine in the art except for specific cells, an artisan of skill would have required undue experimentation to practice the claimed method.

5. Applicants' arguments are moot in view of new grounds of rejection.

6. The double patenting rejections have been withdrawn in view of applicants' arguments.

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on

(703) 305-4051. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

Please note that effective January 13, the offices for Examiner Shukla, SPE Reynolds and LIE William Phillips will move to the new USPTO location in Alexandria, VA and their phone numbers will change. The new phone numbers will be as follows:

Ram Shukla: **(571) 272-0735**

Deborah Reynolds: **(571) 272-0734**

William Phillips: **(571) 272-0548**

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